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10/594,256	09/25/2006	Hanns-Georg Klein	JCLA21973	1260

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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,256	KLEIN, HANNS-GEORG	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-16* is/are rejected.

7)☒ Claim(s) *15 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. Claims 9-16 are pending and will be examined.

Specification

2. The disclosure is objected to because of the following informalities:

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The hyperlinks are present on page 2.

Appropriate correction is required.

Sequence Rules Compliance

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

APPLICANT IS GIVEN the time of response to this office action WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R.. §§ 1.821-1.825. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Applicant submitted sequence listing in paper and computer readable formats, but no letter stating that the two are the same. Further, the specification (page 15) has not been amended to include the SEQ ID NOs.

Claim Objections

4. Claims 15 and 16 are objected to because of the following informalities: the terms "microchip" and "chip" are misspelled as "microship" and "ship", respectively. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 9-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 9-16 are broadly drawn to a method for the prognosis and/or diagnosis of diseases associated with at least one of the polymorphisms 8, 12, 13 in the NOD2/CARD 15 gene by detection of at least one of the polymorphisms Nod2-SNP8, Nod2-SNP12, Nod2-SNP13 in the NOD2/CARD15 gene, wherein the diseases associated with at least one of the polymorphisms 8, 12, 13 in the NOD2/CARD 15 gene are rejection responses occurring after transplantations, graft versus host diseases, host versus graft diseases, sepsis, lung diseases, lymphoma and/or leukemia. However, as will be further discussed, there is no support in the specification and prior art for the methods as claimed. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification has a single working example (pages 14-23), where 169 patients undergoing allogenic stem cell transplantation and their donors were examined for the presence of the three NOD2/CARD15 polymorphisms. The patients were monitored for the presence of graft versus host disease (GvHD) and death in remission (DIR) after one year. The conclusion was that the frequency of total and gastrointestinal GvHD was increased in recipients when the donor, the recipient or both had at least one of the three polymorphisms. Further, the increased risk of death was not only due to the GvHD, but also due to respiratory failure. The results showed similar trends in cases were the donors were either HLA-identical or unrelated. There are no working examples related to the diagnosis of rejection responses occurring after any organ transplantation, graft versus host diseases, host versus graft diseases, sepsis, lung diseases, lymphoma and/or leukemia, or prognosis of rejection responses occurring after any organ transplantations, host versus graft diseases, sepsis, lung diseases, lymphoma and/or leukemia or prognosis of GvHD after stem cell transplantation.

Guidance in the Specification.

The specification provides no evidence that the claimed methods can be performed by one of skill in the art regarding the diagnosis of rejection responses occurring after transplantations, graft versus host diseases, host versus graft diseases, sepsis, lung diseases, lymphoma and/or leukemia, or prognosis of rejection responses occurring after transplantations, host versus graft diseases, sepsis, lung diseases, lymphoma and/or leukemia. Further, a thorough review of the art up to date fails to show any enabled teachings of even prognosis of GvHD in patients undergoing stem cell transplants, as detailed below.

Therefore the guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

The unpredictability of the art and the state of the art

The following two papers, both published at least two years after the priority date of the instant application show that there is a great deal of unpredictability concerning the use of NOD2/CARD15 mutations for prognosis of GvHD after stem cell transplantation. Holler et al. (Blood, vol. 107, pp. 4189-4193, May 2006) examined two cohorts of patients (total of 303) undergoing stem cell transplations in which the donors and recipients were HLA-identical for the presence of the three NOD2/CARD15 mutations in cohort II (225 patients) (Abstract; page 4190, paragraphs 2-5 and Table 1). After examining the incidence of GvHD and transplantation-related mortality at 1 year or overall (TRM), the authors concluded the following (Table 3; Fig. 1; page 4191):

i) stage III/IV GvHD was significantly associated with the presence of at least one mutation in cohort I (78 patients), but not in cohort II;

ii) stage II-IV of GI GvHD was significantly associated with the presence of at least one mutation in cohort II, but not in cohort I;

iii) TRM at 1 year was significantly associated with the presence of at least one mutation in cohort I, but not in cohort II;

iv) overall TRM was significantly associated with the presence of at least one mutation in both cohorts;

v) overall survival (OS) was significantly associated with the presence of at least one mutation in cohort I, but not in cohort II.

Finally, Holler et al. discovered that gastrointestinal decontamination removed the association between the TRM and the presence of one or more of the NOD2/CARD15 polymorphisms (page 4192, first and second paragraph; Table 6; Fig. 2).

Therefore, the only variable which was strongly associated with the presence of the polymorphisms in both cohorts was overall TRM, and even this association depended on the treatment patients received prior to the transplantation.

In a similar vein, Granell et al. (Haematologica, vol. 91, pp. 1372-1376, 2006), examined the effect of NOD2/CARD15 polymorphisms in patients (85, with 71 donors) who underwent allogenic stem cell transplantation in which the donor T-cells were depleted prior to the transplantation. In particular, they looked at the incidence of GvHD, disease-free survival (DFS) time and non-relapse mortality (NRM) (Abstract; page 1373, paragraphs 1-3; page 1374, first paragraph). They concluded that there was no statistically significant association of the presence of any of these polymorphisms with GvHD (page 1374, third paragraph) or NRM (page 1375, first paragraph). The DFS was significantly associated with the presence of the NOD2/CARD15 polymorphisms (page 1374, last paragraph; Fig. 1). The concluded as follows (page 1375, second paragraph):

"In this study we showed that patients with variant alleles of *NOD2/CARD15* undergoing T-cell-depleted allogeneic SCT had a lower disease-free survival than that of patients with the wild-

type genotype. Indeed, this genetic marker was one of the two most important independent prognostic factors for poor disease-free survival in the multivariate analysis. This detrimental effect was not due to an increase in the incidence and severity of GVHD, as previously reported for unmanipulated allogeneic SCT[4,5] since this complication was not associated with the presence of variant alleles of *NOD2/CARD15* in either the donor or the recipient."

Therefore, it is clear from the two references above that parameters other than the presence of NOD2/CARD15 mutations affect the correlation (or lack thereof) with the presence or severity of GvHD in patients undergoing stem cell transplantation.

Finally, Brenmoehl et al. (Intensive Care Med., vol. 33, pp. 1541-1548, 2007) examined the association of sepsis with NOD2/CARD15 gene polymorphisms in 132 patients (Abstract; page 1543, Table 1). The conclusion of this study was that only the Leu1007 (ins C3124, SNP-13) frameshift mutation had statistically significant association with sepsis related mortality (SRM) (Abstract; page 1545, second and third paragraph; Fig. 1).

Therefore, in case of sepsis, only the SNP13 can serve as a prognostic indicator of sepsis related mortality.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this methodology to enable diagnosis and prognosis of rejection responses occurring after transplantations, graft versus host diseases, host versus graft diseases, sepsis, lung diseases, lymphoma and/or leukemia, or prognosis of rejection responses occurring after transplantations, graft versus host disease, host versus graft diseases, sepsis, lung diseases, lymphoma and/or leukemia, including the type of organ undergoing transplantation, the degree of HLA matching between donors and recipients, the effect of different pre-transplantation procedures which the patients undergo, in populations large enough to produce

statistically significant results. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the responses to transplantation depend upon numerous known and unknown parameters the factor of unpredictability weighs heavily in favor of undue experimentation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

7. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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